REMARKS

Claims 1 and 5-7 are amended herein. Support for these amendments can be found throughout the specification, for example, pages 6-9 of the application. No new matter has been added. Claims 17-21 have been previously withdrawn. No claims have been canceled herein. Accordingly, Claims 1-16 are pending. In view of the amendments and remarks set forth herein, reconsideration is respectfully requested.

Point of Novelty

The Examiner has alleged on page 7 of the office action that no point of novelty is seen in the specification and that it is conventional in treating disorders that require multiple drugs to determine the effect of the treatment and alter the treatment accordingly. Applicants respectfully traverse.

The scientific approach to the discovery of new drugs has been based on the developments of methods to isolate and study molecules, evaluating the bioactivity based on a reductionistic way, i.e. studying the performance in target or cell-based assays. The current strategy for the discovery of candidate compounds, obtained via synthesis or isolation from natural sources, designed to interact with a specific molecular target, is to seek ever-more selective compounds for the target by differential in vitro screening of molecules in an array of available 'target-based' assays. For this purpose large drug libraries are developed and used. This so-called target-centric drug discovery approach is as such very time-consuming and costly.

Moreover, many very specific drugs that have been identified using this approach are doomed to failure because of unanticipated effects on 'off-target' biochemical mechanisms and the safety implications of those unwanted, and sometimes fatal, side-effects might not be revealed until a drug candidate is in large-scale clinical trials or even on the market. This is due to the fact that these specific drugs are directed towards a particular target that is only part of the entire pathophysiology of the disease concerned and simply produce improvements in a limited number of symptoms.

It will be clear from the above that the nature of this target-centric drug discovery approach based on single components forms the basis of a huge problem, impacting the timely launch of new successful drugs.

The aim of the present invention is to provide a method that solves the above-discussed problem. Surprisingly, it has been found that this can be realized in a most effective manner when use is made of an approach that differs essentially from the target-centric drug discovery approach. This new approach is embodied in the present invention which enables highly detailed profiling and subsequent measurements of multicomponent induced changes in biological systems (biological effects) such as in-vitro (e.g. cell-cultures) and in particular in-vivo systems (e.g. animal models, humans). Intervention is based on the synergetic nature of multiple components at the system level, and as until the present invention no technology or strategy had been invented that enables the discovery of a set of synergetic components in a multicomponent

synthetic product that in concert provides regulation of a biological system towards a health status.

In the method according to the present invention, the interaction of multiple components with living biological systems can very effectively be measured, using a particular set of steps wherein technologies are applied such as biostatistics and bioinformatics. In this method, the interaction of multiple synthetic components with living biological systems can very effectively be measured, using a particular set of steps wherein technologies are applied such as biostatistics and bioinformatics.

By means of the measurements according to the present invention, the impact of multicomponent mixtures on the biological profile of a disease can advantageously be determined. Moreover, such measurements enable the choice of effective and safe components within multicomponent mixtures, and their-respective concentrations required for having an impact on the biological profile of the disease can be identified. In other words, in the present method the interaction of multiple components with living biological systems can be measured, whereas, in stark contrast in the conventional target-centric drug discovery approach, the biological outcome of usually a very large number of single candidate compounds or a large number of random combinations of two candidate compounds is measured, on the basis of a drug/chemical compound library, at a molecular or a cellular level. Hence, as will be

immediately appreciated by the skilled person the present method substantially differs from the known target-centric drug recovery approach.

It cannot be emphasized enough that that the present invention provides the measurement at a **systems level** which is crucial for almost all multifactorial diseases, not at a molecular or cellular level whereby the focus is on a particular, usually acute, symptom. In this respect it is observed that the early start of a disease is often characterized by a shift in balance between different organizational structures in a system and biochemical communication and control signals are typically found at a systems level not a single cell type level. Clearly at increasing levels of complexity in a system new properties are evolving. This communication and control element is found among others in body fluids present in a system such as blood, CSF or reflections thereof in urine. The present invention enables the discovery of system descriptors, biomarkers describing lower and higher levels of organization and control, and uses this information to optimize multicomponent synthetic product mixtures to address the disregulation at different pathways and different system levels.

Hence, the method according to the present invention enables the measurement of the effects of multiple target interventions and the development of products to optimally perform such interventions by a unique approach, revealing the biological profile of the effective components. In this unique approach biological systems are studied by measuring and integrating metabolic data and other profile data, such as genetic and/or proteomic data.

As will be clear from the above, the present invention stands in stark contrast with the conventionally target-centric drug discovery approach. It can only be concluded that the present invention provides a unique solution to the problem associated with the conventional target-centric drug discovery approach. The present invention constitutes a considerable and major improvement over the prior art, not only in technical terms, but also in view of cost-effectiveness and the benefits for society at large.

Double Patenting

Claims 1-16 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/570,505. Applicants request that the Examiner hold the provisional rejections made under the judicially created doctrine of obviousness-type double patenting in abeyance until otherwise allowable subject matter is identified in the instant application. Once allowable subject matter has been identified, Applicants will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time.

Claim Rejections under 35 U.S.C. §102

Claims 1-16 are rejected under 35 U.S.C. §102(a) as being anticipated by Afeyan et al. (US 2005/0273275). Applicants traverse the rejection.

Afeyan et al. was published on December 8, 2005 and the PCT filing date of the present application is September 3, 2004 with a priority date of September 5, 2003. Therefore, Afeyan et

al.is not prior art under § 102(a). Afeyan et al. (US 2005/0273275) is, however, a divisional application of US 2003/0134304, published July 17, 2003 which the Examiner may cite in his next office action. Alternatively, the Examiner may have intended to issue the rejection as a §102(e).

Nevertheless, nothing in Afeyan et al. teaches or discloses steps (b) to (d) of the pending claims. The Examiner cites to paragraphs 4 and 5 of Afeyan et al. for teaching developing drugs for diseases with multiple biomarkers and profiling with mass spectrometry. In contrast, the claims are directed to a method for determining the impact of a multicomponent synthetic product mixture on a biological profile of a disease. Nothing in Afeyan et al. teaches the claimed methods.

Furthermore, nothing in Afeyan et al. teaches all of the methods steps included in the claims, in particular steps (b) to (d). Afeyan et al. do not disclose each and every element of the pending claims and thus fails to anticipate the pending claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections Under 35 U.S.C. §103

Claims 1-16 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Borisy et al. Applicants respectfully traverse the rejection.

The Examiner cites to Example 3 and table 1 of Borisy et al. Example 3 describes the effect of drug pair-wise combinations on cell proliferation. Borisy et al. therefore, relate to a target-centric method for identifying drug-drug interactions and uses as basis pure components. Consequently, said method differs totally from the present invention, and said method is limited to purified molecules from which only partial synergetic information can be obtained by random screening efforts. Borisy et al. clearly do not teach or suggest a method wherein the impact of a multicomponent synthetic product mixture is determined on the profile of a disease within a group of living systems. Furthermore, Borisy et al. do not disclose a method wherein the determination of a biological profile of a disease within a group of living systems is combined with the determination of a profile of a multicomponent synthetic product mixture that displays a desired impact on the profile of the disease.

At best Borisy et al. teach the impact of a particular combination of two drugs on a particular symptom of a disease within a sub-system of a whole organism (see [0079]-[0081]). It does not teach the impact of a multicomponent synthetic product mixture on a the biological profile of a disease as such within a living system nor does it provide any technology that is capable of measuring such information.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicants submit that nothing in the cited references, alone or in combination, teach all of the claim limitations. As nothing in the cited references teach or suggest the subject-matter of the claims, the cited references fail to render the claims obvious.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

35 U.S.C. §112, 1st Paragraph Written Description

Claims 1-16 are rejected under 35 U.S.C. first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The disclosure in the application as filed clearly demonstrates Applicants' possession of the claimed invention. The Example described on page 13 describes a typical experiment of how to implement the claimed methods. Furthermore the determination of a biological profile of a disease from step (a) of claim 1 is described, e.g., on page 6, lines 21-31. The determination of the impact from step (b) is described, e.g., in the paragraph bridging pages 6-7. Steps (c) and (d)

are described, e.g., on page 7, lines 6-11. Multivariate analysis is described throughout the application, in particular on page 9, line 14 to page 11, line 25.

Based on the above remarks, Applicants submit that the claims meet the written description requirements under 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-16 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Regarding Claim 1, the Examiner alleges a lack of antecedent basis for the term "the impact". However, Applicants submit that the impact on a biological profile is an inherent component of a multicomponent synthetic product mixture and a series of samples. Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. MPEP 2173.05(e)

The Examiner states that what may be intended by "a group of living systems" is not seen. Applicants submit that in light of the specification (see, e.g., page 2, lines 5-8; page 3, lines 21-23) a skilled person would understand the scope of the claim.

The Examiner states that in claim 1(b) how the determining is performed is not set forth. Claim 1(b), in fact, refers to the use of a multivariate analysis, which is well described in the application (see, e.g., page 9, line 14 to page 11, line 25). Applicants submit that in light of the specification, a skilled person would understand the scope of the claim.

The Examiner states that the term "(trace) elements" is not understood in claim 14. Applicants submit that trace elements is a well-known term in the medical/biological arts and a skilled person would therefore clearly understand the scope of the claim. In an effort to expedite prosecution "(trace) element" has been amended to "trace elements."

In an effort to expedite prosecution, the following amendments have been also made which are believed to obviate the remaining rejections. The term "the biological profile" in claim 1 has been amended to "a biological profile". The term "information obtained" in claim l(c) has been amended to "impact determined". Claim 5 has been amended to refer to the use for determining "the impact of the set of multicomponent mixtures on the biological profile of the disease". Claim 7 has been amended to more particularly describe the claimed subject-matter.

Accordingly, it is now believed that this application is in condition for further consideration and examination. If resolution of any remaining issues is required prior to the

examination of the application, it is respectfully requested that the examiner contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

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